Pain Control in Total Knee Arthroplasty

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Abstract

As surgical techniques and pharmacology advance, the management of postoperative pain in patients undergoing total knee arthroplasty (TKA) continues to evolve. The current standards of care are composed of multimodal pain management including opioids, nonsteroidal anti-inflammatory drugs and gabapentinoids, peripheral nerve blocks, and periarticular injections. Newer modalities are composed of delayed release local anesthetics and cryoneurolysis. To summarize the current evidence-based treatment modalities and forecast changes in the management of patients having TKAs, we reviewed available data on: (1) oral analgesics; (2) periarticular injections; (3) peripheral nerve blocks; (4) multimodal regimens; and (5) newer modalities in post-TKA pain management. Multimodal analgesic regimens that target numerous pain pathways may provide the best pain management, rehabilitation, patient satisfaction, and reduce opioid use and related side effects. Periarticular injections of delayed-release local anesthetics may further enhance pain management.

Keywords
- total knee arthroplasty
- multimodal pain management
- oral analgesics
- periarticular injections
- peripheral nerve blocks

Postoperative pain after total knee arthroplasty (TKA) remains a significant clinical challenge. The pain impairs recovery and rehabilitation, and may lead to prolonged hospitalization and higher associated costs.[1–3] Establishing an optimal analgesic regimen requires continuous re-evaluation of the available data. After general or spinal anesthesia, the pain management often consists of epidural, intrathecal, and patients controlled analgesia. Oral and intravenous opioids also continue to play a primary role in postoperative pain relief due to their effectiveness in relieving moderate to severe pain. However, because of their unfavorable side-effect profile,[4] combinations of newer alternative therapies, as well as variable oral analgesics, such as cyclooxygenase 2 (COX-2) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), and gabapentinoids have been used to supplement, as well as replace frequent opioid use. Peripheral nerve blocks and periarticular injections are also common modalities.[5] One such periarticular injection is liposomal bupivacaine, which is a delayed release local anesthetic that has a slow release over ~96 hours.[6–11]

The purpose of this review was to summarize the data on the efficacy of commonly used modalities for the management of immediate postoperative pain following TKA. Specifically, we evaluated the literature on: (1) oral analgesics; (2) periarticular injections; (3) peripheral nerve blocks; (4) multimodal pain regimens; and (5) newer pain modalities described in recent studies in patients who underwent TKA.

Materials and Methods

The literature was reviewed through three electronic databases: PubMed, EBSCOhost, and Scopus. This search was performed in January 2017 by two authors (R.K.E. and A.K.). We

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evaluated studies published between 1989 and 2016 using the following search terms: arthroplasty*[title], knee [title], postoperative pain [title], analgesia [title], peripheral nerve block [title], femoral nerve block (FNB) [title], adductor canal block (ACB) [title], liposomal bupivacaine [title], and periarticular injection [title]. Other search terms included: "postoperative analgesia," "multimodal drug injection," "knee arthroplasty," "knee replacement," "oral analgesia," "local infiltration analgesia," and "sciatic nerve block." We included all relevant reports on intraoperative and postoperative analgesic regimens in TKA; nonpeer-reviewed literature and articles in language other than English were not reviewed. Specifically, we isolated studies that assessed opioids, acetaminophen, NSAIDs, neuroleptic agents, serotonin–norepinephrine reuptake inhibitors (SNRI), periarticular injections, peripheral nerve blocks, cryoneurolysis, and long-acting local anesthetics. We attempted to include as many Levels I and II studies; however, all studies thought to be relevant to our topic were included.

Oral Analgesics

Oral analgesics are often the mainstay of treatment in the immediate- to short-term postoperative period. Despite the effectiveness of opioids, they often lead to undesirable side effects such as vomiting, constipation, confusion, and respiratory depression,[4,12] which has led to a shift toward alternative and multimodal analgesia regimens, such as acetaminophen, NSAIDs, and neuroleptic agents (e.g., gabapentin and pregabalin), as a part of pre-emptive or postoperative pain management.

Acetaminophen is often used as the initial step in multimodal pain control. Politi et al compared oral to intravenous acetaminophen (1 g preoperatively and then postoperatively every 6 hours for 24 hours in both cohorts) used in 120 total joint arthroplasty patients and reported that there were no differences in 24 hours postoperative visual analog scale (VAS) scores or hydromorphone equivalent doses utilized.[13]

Anti-inflammatory agents (NSAID) suppress prostaglandin and the inflammatory process by inhibiting COXs. Because of their nonspecific action on prostaglandins, they have been associated with serious side effects, such as gastric erosions and ulcers.[4] There have also been concerns with the use of nonspecific NSAIDs after TKAs due to a possible inhibitory effects on bone healing, reduced fracture healing, inhibited bone ingrowth on implant surfaces, and suppressed postexercise protein synthesis in skeletal muscle.[14–18] Alternatively, selective COX-2 inhibitors have been used, which inhibit prostaglandins with only minimal effects on the gastric mucosa, thus reducing the side effects associated with traditional NSAIDs.[14]

In summary, NSAIDs have been used in the management of pain following TKA, both pre-emptively and postoperatively. Additional consideration for their use is described in the following sections.

Pre-emptive Oral Analgesia

The concept of pre-emptive analgesia is based on the theory that the administration of analgesia prior to the introduction of a nociceptive stimuli provides better pain control than administration of it after the stimuli.[19] Both preincisional and postincisional administration of analgesia is considered to be pre-emptive, since factors such as retraction, tissue manipulation, and postoperative inflammation also contribute to acute and long-term pain.[20] Various analgesic interventions have been studied, including epidural and local analgesics, N-methyl-D-aspartate antagonists, NSAIDs, opioids, and their combinations. The purpose of pre-emptive analgesia in TKA patients is to modulate sensitization of the peripheral and central pain pathways by reducing the production of inflammatory chemicals associated with surgery.[21] As a part of the enhanced recovery after surgery protocols,[22] pre-emptive oral analgesia has been advocated as a part of the multimodal approach to optimize post-TKA outcomes.[23] These include combinations of oral acetaminophen, opioids, NSAIDS, specifically COX-2 inhibitors, pregabalin, and gabapentin.

Several studies have evaluated the use of pre-emptive analgesia before surgery to alleviate pain (►**Table 1**). Munteanu et al[24] randomized 165 patients randomized to receive either pre- (120 mg etoricoxib 1 hour before surgery, placebo after surgery, and 120 mg etoricoxib 24 hours after surgery) or postoperative etoricoxib (placebo 1 hour before surgery, etoricoxib 120 mg after surgery and 24 hours after surgery), or placebo. The authors noted that the 48-hour opioid consumption was lower in those who received pre- versus postoperative etoricoxib (44 vs. 52 mg; $p = 0.002$), with no significant differences in side effects between the groups. Mallory et al[25] evaluated the use of epidural analgesia with

Table 1 Pre-emptive oral analgesia

Author (year)	Type of analgesia	Mode of analgesia	No. of patients	Pain score	Opioid consumption (mg)
Munteanu et al[24] (2016)	Cox-2 inhibitor	Pre-emptive vs. postoperative	165	N/A	44 vs. 52, $p = 0.002$
Mallory et al[25] (2002)	Cox-2 inhibitor	Epidural alone vs. epidural and pre-emptive vs. spinal and pre-emptive	251	Lower breakthrough pain in epidural and pre-emptive ($p = 0.009$)	N/A
Buvanendran et al[26] (2010)	Pregabalin vs. placebo	Pre-emptive	240	Neuropathic pain: 0 vs. 8.7%, $p = 0.01$	4.5 vs. 7.3, $p = 0.005$

Abbreviations: COX-2, cyclooxygenase 2; N/A, not applicable; VAS, visual analog scale.

and without the addition of a pre-emptive COX-2 inhibitor in 251 patients. Patients who received pre-emptive analgesia had lower reports of breakthrough pain ($p = 0.009$), nausea ($p = 0.047$), and confusion ($p = 0.01$) compared with those who received epidural analgesia alone.

Buvanendran et al[26] randomized 240 patients to receive preoperative pregabalin (300 mg prior to TKA and 150–50 mg twice daily for 14 days after TKA) or placebo. Postoperatively, patients who received pregabalin had a lower incidence of neuropathic pain (0 vs. 8.7%; $p = 0.001$) and lower opioid use ($p = 0.005$), when compared with the placebo cohort, although they had a higher incidence of sedation ($p = 0.005$) and confusion ($p = 0.013$).

In summary, the use of pre-emptive oral analgesia prevents sensitization and hyperexcitability, which may improve analgesia following TKA. Various classes of medications have been studied and show promising results.

Postoperative Oral Analgesia

Nonsteroidal Anti-inflammatory Drugs

Gong et al[27] conducted a randomized, double-blind study comparing the effect of celecoxib (300 mg twice daily) versus placebo on the amount of opioid use in 150 TKA patients. Postoperatively, patients in the celecoxib cohorts (with and without a muscle relaxant) had significantly reduced opioid consumption compared with the placebo cohort (198 vs. 225 vs. 255 mg; $p = 0.0001$). The authors also found that VAS scores were lower at 7 days postoperatively (2.0 vs. 2.7 vs. 3.4 points; $p = 0.0005$). Kazerooni et al[28] retrospectively evaluated 81 TKA patients, who received a FNB with a continuous catheter, and were allocated to receive either twice daily celecoxib (200 mg) or no celecoxib. Patients who received celecoxib had lower opioid consumption (203 vs. 336 mg) and VAS scores (2.77 vs. 3.33 points; $p < 0.05$), than those who did not receive celecoxib. The addition of celecoxib to multimodal drug therapy may reduce overall opioid consumption and postoperative pain.

Neuroleptics

Gabapentin, pregabalin, and selective SNRIs may aid in the treatment of neuropathic and postsurgical pain.[29,30]

Jain et al[29] evaluated the effects of pregabalin in 40 TKA patients in a prospective, randomized study, where patients were allocated to receive either pregabalin (75 mg twice daily) or placebo (twice daily). The pregabalin group had lower opioid consumption (3.6 vs. 7.2 mg; $p < 0.05$) and reduced postoperative pain (assessed with 11-point verbal rating score) (3 vs. 4.3 points; $p = 0.001$) compared with the placebo cohort. Furthermore, patients in the pregabalin cohort had lower use of patient controlled epidural anesthesia in the first 24 hours compared with the placebo cohort (17 vs. 40 mg; $p < 0.001$). In addition, Clarke et al[30] conducted a randomized, double-blind study on 179 TKA patients who were allocated to receive either gabapentin (single dose 600 mg preoperatively and 200 mg three times a day for 4 days postoperatively) or placebo perioperatively. In the first 24 hours, there were no significant differences in function or pain scores between the groups, but the gabapentin cohort had significantly lower morphine consumption compared with the placebo group (3.5 vs. 4.5 mg; $p < 0.05$). However, Hamilton et al[31] performed a meta-analysis on the use of gabapentinoids post-TKA and noted that reductions in pain scores and opioid consumption were minimal and not clinically relevant. Furthermore, they advocated against the routine use of these analgesics in the acute postoperative period.

Serotonin–Norepinephrine Reuptake Inhibitors

Few studies have demonstrated the use of the SNRI duloxetine in post-TKA patient. Ho et al[32] prospectively evaluated 50 TKA patients who were randomized to receive either duloxetine (60 mg 2 hours prior to surgery and on first postoperative day) or placebo. The duloxetine group had lower morphine requirement at 24 (13 vs. 20 mg) and 48 hours (20 vs. 30 mg; $p = 0.039$) postoperatively compared with the placebo group. However, there were no significant differences in pain scores between the two cohorts.

In summary, the use of alternative oral analgesia as adjuncts in the postoperative period may improve pain while reducing opioid requirements (►**Table 2**). This includes anti-inflammatory, neuroleptic, and SNRI medications. Virtually all oral analgesics reduced opioid consumption in postoperative period, including celecoxib and pregabalin.

Table 2 Postoperative oral analgesia

Author (year)	Type of analgesia	Mode of analgesia	No. of patients	Pain score	Opioid consumption (mg)
Gong et al[27] (2013)	Cox-2 inhibitor with/without muscle relaxant vs. placebo	Postoperative	150	VAS: 2.0 vs. 2.7 vs. 3.4, $p = 0.0005$	198 vs. 225 vs. 255, $p = 0.0001$
Kazerooni et al[28] (2012)	Cox-2 inhibitor	Postoperative	81	VAS: 2.77 vs. 3.33, $p = 0.002$	203 vs. 337, $p < 0.05$
Jain et al[29] (2012)	Pregabalin vs. placebo	Postoperative	40	VRS: 3 vs. 4.3	3.6 vs. 7.2, $p < 0.05$
Clarke et al[30] (2014)	Gabapentin vs. placebo	Pre- and postoperative	179	4.2 vs. 4.3, $p = 0.836$	3.5 vs. 4.5, $p < 0.05$
Ho et al[32] (2010)	Duloxetine vs. placebo	Pre- and postoperative	50	N/A	24 h: 13 vs. 20, $p = 0.039$ 48 h: 20 vs. 30, $p = 0.017$

Abbreviations: COX-2, cyclooxygenase 2; N/A, not applicable; VAS, visual analog scale; VRS, verbal rating score.

Periarticular Injections of Local Anesthetics

Periarticular injections are an alternative method for pain control during TKA (►**Table 3**). Their use is advocated due to the ease of use while avoiding potential neurologic complications, quadriceps muscle weakness and falls associated with nerve blocks, and the systemic effects of oral analgesics.[33–36] These injections are composed of a single or several multimodal drugs, which will be discussed in the following sections.

Periarticular Injections of Various Mixtures

Multimodal periarticular or intra-articular injections were initially widely utilized by Maheshwari et al.[42–44] In conjunction with Parvataneni et al,[44] they advocated for a multimodal injection consisting of 0.5% bupivacaine (200–400 mg), morphine sulfate (4–10 mg), epinephrine 1/1,000 (300 µg), methylprednisolone acetate (40 mg), and cefuroxime (750 mg). Patients who received this were compared with a control cohort who received a FNB and patient controlled analgesia (PCA). Pain scores were significantly lower in the injection group on postoperative day (POD) 1 (3.8 vs. 5.6 points; $p < 0.05$), POD 2 (2.8 vs. 4.1 points; $p < 0.05$), and POD 3 (2.6 vs. 4.5 points; $p < 0.05$) when compared with the control cohort.

Motififard et al[38] conducted a double-blind, randomized trial comparing an injection mixture of bupivacaine, morphine, epinephrine, and ketorolac to an injection of epinephrine only, in a cohort of 137 patients. The injections were given 15 minutes prior to incision. The authors noted improvement in VAS scores at 24 hours (6.3 vs. 8.8 points; $p < 0.001$), 48 hours (5 vs. 6 points; $p = 0.001$), and 6 weeks (3.5 vs. 4.1 points; $p = 0.02$) postoperatively in the mixture group compared with the control cohort. There were significant improvements in Knee Society scores (KSS) at 6 weeks when comparing the study to the control cohort (113.6 vs. 99.8 points; $p < 0.001$). The authors also noted that range of motion was significantly higher in the mixture cohort compared with the control cohort at 24 hours (107 vs. 94 degrees; $p < 0.001$), 48 hours (113 vs. 96 degrees; $p < 0.001$), and 6 weeks postoperatively (127 vs. 120 degrees; $p < 0.001$). In addition, Busch et al[45] conducted a randomized study evaluating the effect of periarticular injections (400 mg ropivacaine, 30 mg ketorolac, 5 mg epimorphine, and 0.6 mL of epinephrine 1:1,000) on postoperative use of PCA in 64 patients. Patients who received periarticular injections had lower total PCA use (25 vs. 43 mg; $p < 0.001$), and more satisfaction scores (measured with VAS) (75 vs. 55 points; $p = 0.013$) and lower postoperative pain scores (measured with VAS) (35 vs. 55 points; $p = 0.007$) at 4 hours postoperatively, than those who did not receive periarticular injections. However, there were no differences in overall opioid analgesic consumption.

Lamplot et al[1] compared the use of a regimen consisting of multimodal periarticular injection (30 mL 0.5% bupivacaine, 10 mg morphine sulfate, and 15 mg ketorolac) and oral analgesics (oxycodone 10 mg every 12 hours, tramadol 50 mg every 6 hours, ketorolac 15 mg parenterally every 12 hours, and oral hydrocodone 5 mg as needed) to hydromorphone PCA and parenterally (1 mg) as needed in 36 patients. Patients who received the multimodal regimen had a lower total narcotic consumption (31 vs. 72 mg; $p < 0.05$), lower VAS scores (2.5 vs. 5 points; $p < 0.01$), and higher satisfaction scores (4.1 vs. 5 points; $p < 0.05$) than the PCA cohort. Similarly, Kwon et al[46] randomized 76

Table 3 Periarticular Injections

Author (year)	Modality	No. of patients	Pain score (VAS)	Opioid consumption (mg)
Sporer and Rogers[37] (2016)	Low-dose liposomal bupivacaine + FNB vs. high-dose liposomal bupivacaine	597	3.2 vs. 3.6, $p = 0.003$	N/A
Motififard et al[38] (2017)	PAI bupivacaine+ morphine + epinephrine + ketorolac vs. PAI epinephrine	137	24 h: 6.3 vs. 8.8, $p < 0.001$ 48 h: 5 vs. 6, $p = 0.001$ 6 wk: 3.5 vs. 4.1, $p = 0.02$	N/A
Lamplot et al[1] (2014)	PAI bupivacaine + ketorolac vs. hydromorphone PCA	36	2.5 vs. 5, $p < 0.01$	31 vs. 72, $p < 0.05$
Bagsby et al[39] (2014)	Liposomal bupivacaine vs. PAI ropivacaine + morphine+ epinephrine	150	4.9 vs. 4.4, $p = 0.04$	79 vs. 66, $p = 0.19$
Barrington et al[40] (2017)	Liposomal bupivacaine + intrathecal bupivacaine vs. intrathecal morphine + PAI ropivacaine vs. PAI ropivacaine + intrathecal bupivacaine	119	Liposomal bupivacaine vs. PAI ropivacaine at 6 h (1.8 vs. 3.3, $p = 0.005$), and 12 h (1.5 vs. 3.3, $p < 0.001$) Intrathecal morphine vs. liposomal bupivacaine at 6 h (0.9 vs. 1.8, $p = 0.035$)	Mean total narcotics consumed: 71 vs. 79 vs. 75, $p = 0.910$
Dysart et al[41] (2016)	Liposomal bupivacaine vs. bupivacaine		Pending results	Pending results

Abbreviations: FNB, femoral nerve block; N/A, not applicable; PAI, periarticular injection; PCA, patient controlled analgesia; VAS, visual analog scale.

women post-TKA to receive either a multimodal periarticular injection (10 mg morphine, 300 mg ropivacaine, 30 mg ketorolac, and 300 µg epinephrine 1:1,000) with corticosteroid or without, and on POD 0, patients who received the added corticosteroid had significantly lower VAS scores than those who received the injection alone (1.2 vs. 2.3 points; $p = 0.021$), but no significant difference were found thereafter.

In a meta-analysis of 21 randomized, controlled trials, Jiang et al[3] evaluated the effect of periarticular multimodal drug injection (PMDI) on TKA patients. The various studies incorporated combinations of ropivacaine or bupivacaine with or without epinephrine, an NSAID, and a corticosteroid. When compared with placebo, VAS scores at 6 and 24 hours were lower in those patients who had PMDI ($p < 0.05$). Furthermore, those who had the PMDI had lower opioid consumption at 24 hours postoperatively ($p < 0.05$). However, there was no difference in lengths of stay between the cohorts. In a meta-analysis by Teng et al,[47] it was noted that PMDI allowed for short-term reduction in VAS scores, up to POD 3, as well as lower overall narcotic consumption.

In summary, periarticular injections of "multimodal" mixtures decreased postoperative pain scores, improved functional outcomes, range of motion, and lowered opioid consumption. However, each study used a heterogeneous combination of medications, making it difficult to make the ultimate recommendation.

Liposomal Bupivacaine

Liposomal bupivacaine, a suspension of lipid-based vesicles allows for slow diffusion of bupivacaine, by up to 96 hours after infiltration, and may allow for longer acting analgesia than injection of bupivacaine alone.[39,48–51] Sporer and Rogers[37] evaluated 597 TKA patients, who received either bupivacaine FNB and low-dose liposomal bupivacaine or high-dose liposomal bupivacaine (266 mg) alone. Patients who received high-dose liposomal bupivacaine alone had a lower need for breakthrough pain medication (17 vs. 36%; $p < 0.001$), decreased VAS scores at 12 hours postoperatively (3.2 vs. 3.6 points; $p < 0.003$), and earlier time to ambulation (30 vs. 32 hours; $p < 0.17$) compared with the combined nerve block and liposomal bupivacaine group. These findings are supported by Bramlett et al,[50] who conducted a randomized, double-blind study on 138 TKA patients to assess the effects of varying doses (133, 266, 399, and 532 mg) of liposomal bupivacaine compared with the traditional periarticular bupivacaine injection for postoperative pain and opioid consumption. The authors reported that only the high-dose group (522 mg) had a significant improvement in cumulative pain scores (measured by area under the curve) on POD 5 (10 vs. 16 units; $p < 0.05$), compared with the traditional bupivacaine injection. Dasta et al[52] compared the effect of liposomal bupivacaine (266 mg) to traditional periarticular bupivacaine injection (up to 200 mg) (control) and noted that liposomal bupivacaine patients had lower opioid consumption than the control group on POD 3 (12.2 vs. 19 mg; $p < 0.0001$). Similarly, Barrington et al[40] conducted a multicenter randomized trial on 119 TKA patients and noted similar pain control between liposomal bupivacaine and intrathecal morphine, and thus advocated for the use of the liposomal bupivacaine due to an improved side-effect profile.

The use of liposomal bupivacaine may also lead to shorter hospital stays. Chughtai et al[9] evaluated a large hospital database of 94,828 TKA patients who either received liposomal bupivacaine or no periarticular injection. The authors noted that patients who received the liposomal bupivacaine had significantly shorter lengths of stays (2.6 vs. 3 days; $p < 0.05$) and higher incidences of home discharges (73 vs. 67%). Kirkness et al[7] also retrospectively assessed the effect of ACB and liposomal bupivacaine compared with FNB in 237 TKA patients. The authors noted that the groups who received the liposomal bupivacaine had greater walking distances postoperatively and shorter mean lengths of stay than the FNB group ($p < 0.05$).

Some studies have shown results that differ, which may have limitations related to the techniques used in the administration of the liposomal bupivacaine. Bagsby et al[39] retrospectively reviewed 150 TKA patients who received either a multimodal periarticular injection, consisting of ropivacaine, morphine, and epinephrine, or liposomal bupivacaine (266 mg added to 30 mL normal saline to a total of 50 mL, needle gauge was not specified). There were no significant differences in mean opiate usage between the two cohorts. The VAS pain scores were higher in the cohort injected with liposomal bupivacaine compared with the multimodal injection throughout the hospital stay (4.9 vs. 4.4 points; $p = 0.04$). Similarly, Jain et al[53] evaluated 207 consecutive patients who were randomized into three groups: periarticular liposomal bupivacaine (266 mg, diluted to 60 mL, injected using 22-gauge needle), periarticular bupivacaine and morphine, and intra-articular bupivacaine and morphine. There were no significant differences in postoperative VAS scores among the three cohorts at 24 hours postoperatively. However, liposomal bupivacaine is a delayed-release formulation that releases bupivacaine over 72 hours or longer. Alijanipour et al[54] randomized 162 patients to receive either liposomal bupivacaine (266 mg, diluted with 40 mL of normal saline and 0.5 mL of epinephrine 1 mg/mL, injected using 18-gauge needle) or periarticular free bupivacaine. The authors noted no significant differences in postoperative pain scores, opioid consumption, KSS, or 12-item Short Form Survey scores ($p > 0.05$). The earlier studies may have been limited because of the nonstandard techniques, which is important for the efficacy of the medication. The total volume of liposomal bupivacaine after dilution varied in these studies. In addition, injection technique was not described in enough detail. Manufacturer recommends using a smaller gauge needle (20 vs. 18 gauge) and multisite injection technique.

In summary, analgesia with liposomal bupivacaine has been demonstrated in many studies in patients who underwent TKA. Although some studies reported no difference in pain control between liposomal bupivacaine and the standard of care, Khlopas et al[55] suggested that there may be a learning curve associated with its use. Therefore, conflicting results in the literature may be attributed to varying techniques of administration, which necessitates a standardized

protocol for intraoperative injection to achieve optimal results. A phase 4, prospective, randomized, double-blind, controlled, parallel-group study with more than 10 participating centers is underway aiming to evaluate safety and efficacy of liposomal bupivacaine as compared with standard bupivacaine in patients undergoing TKA.[41]

Peripheral Nerve Blocks

Several peripheral nerve blocks have been used to accomplish analgesia after TKA, such as FNBs, ACBs, femoral triangle blocks, obturator nerve blocks, and sciatic nerve blocks (►**Table 4**). These can be administered as a continuous infusion or as a single shot, which will each be described.

Femoral Nerve Block

FNBs are one of the more commonly used peripheral nerve blocks for analgesia after TKA.[60,61] Although both single-shot and continuous blocks have been used, continuous blocks results in lower opioid consumption.[62]

Paul et al[59] evaluated 23 randomized controlled trials comparing the effect of FNB and PCA opioids in TKA. At 24 hours postoperatively, patients who received either a single-shot or continuous FNB had significantly lower morphine consumption than those using a PCA (−20 and −15 mg; $p < 0.05$), as well as at 48 hours (−38 and −24 mg; $p < 0.05$) postoperatively. Those who received the single-shot or continuous FNB also had lower pain scores at 24 (−1.8 vs. −1.5 points; $p < 0.05$) and 48 hours (−1.5 vs. −1.3 points; $p < 0.05$), compared with PCA. In addition, FNB has been shown to have superior outcomes compared with epidural analgesia. A prospective randomized controlled trial by Sakai et al[63] evaluated 66 TKA patients who received continuous FNB versus continuous epidural analgesia. The FNB group had improved knee range of motion (115 vs. 103 degrees; $p < 0.001$) and significantly earlier discharge (4 vs. 5 days; $p = 0.002$) than the epidural cohort. However, resting VAS scores were found to be comparable between both cohorts.

Studies have also compared the use of continuous versus single FNBs. Choi et al[64] conducted a randomized trial comparing continuous FNB, single FNB, and local infiltration analgesia in 168 TKA patients. The authors noted that on POD 1, the continuous FNB and local infiltration groups had greater improvements in pain compared with the single FNB group, but no significant differences in pain scores or opioid consumption between the groups on POD 2. Similarly, Chan et al[65] conducted a randomized study comparing the effect of single and continuous FNB versus a control group (PCA) on postoperative pain in 200 TKA patients. They noted that those patients who received continuous FNB had the lowest opioid consumption ($p < 0.05$), but there were no significant differences in VAS pain scores between the continuous and single FNB groups, although both were significantly lower than the PCA cohort ($p < 0.05$).

Although FNBs may provide effective analgesia, studies have shown decreased muscle strength postoperatively, and a subsequent increased risk of falling. Jaeger et al[61] demonstrated better quadriceps muscle strength following ACBs than FNB in 11 healthy volunteers. In this study, the FNB reduced the quadriceps muscle strength by 49% compared with the placebo. Similar results were reported by Kwofie et al,[34] who noted a significant decrease in quadriceps muscle strength (95 vs. 11%; $p < 0.05$) when compared with ACBs. These studies highlight that FNB may lead to muscle weakness, with a possible increase in fall risk; therefore, a fall precautions protocol should be implemented.

Sciatic Nerve Block

A sciatic nerve block is occasionally performed in conjunction with a FNB to provide an analgesic effect to the posterior aspect of the leg and knee.

Abdallah et al[57] conducted a randomized study demonstrating that a sciatic nerve block in conjunction with a FNB may provide improved pain relief. Patients who received the FNB with a proximal or distal sciatic nerve block had a lower proportion of severe knee pain when compared with those who received the FNB alone (12 vs. 17 vs. 78%; $p < 0.001$). However, these differences did not last beyond 6 hours postoperatively. Paul et al[59] demonstrated no differences in pain scores between patients who received a single-shot FNB with sciatic nerve block, single-shot FNB alone, and continuous FNB. However, patients with the combined block had significantly lower morphine consumption (−11 vs. −16 mg; $p < 0.05$) following TKA.

Conversely, Al-Zahrani et al[66] compared continuous FNB with sciatic nerve block versus epidural analgesia in 50 TKA patients, and found that there were no significant differences

Table 4 Peripheral nerve blocks

Author (year)	Modality	No. of patients	Pain score (VAS)	Opioid consumption (mg)
Nader et al[56] (2016)	ACB bupivacaine vs. placebo	40	N/A	40 vs. 60, $p = 0.03$
Abdallah et al[57] (2014)	Sciatic + FNB vs. FNB	53	17 vs. 78% reduction, $p < 0.001$	N/A
Jenstrup et al[58] (2012)	ACB ropivacaine vs. placebo	75	40 vs. 60 points, $p = 0.01$	40 vs. 56, $p = 0.006$
Paul et al[59] (2010)	FNB single-shot vs. continuous vs. PCA	N/A	Single and continuous shot 24 h: 1.8 and 1.5 reduction, $p < 0.05$ 48 h: 1.5 and 1.3 reduction, $p < 0.05$	Single and continuous shot 24 h: −38 and −24, $p < 0.05$; at 48 h: −38 and −24, $p < 0.05$

Abbreviations: ACB, adductor canal block; FNB, femoral nerve block; N/A, not applicable; PCA, patient controlled analgesia; VAS, visual analog scale.

in pain scores or opioid consumption between the two modalities. Although adding sciatic nerve block to a FNB provides analgesia equivalent to epidural analgesia, the resulting motor paralysis may interfere with ambulation.

Adductor Canal Block

ACB has been shown to provide analgesia after TKA, while preserving quadriceps muscle function better than FNB.[61]

Several studies have demonstrated that ACB may provide better analgesia and lower opioid consumption compared with placebo, and sometimes as equally effective as FNB.[58,67–69] Jenstrup et al[58] conducted a double-blind study on 75 TKA patients who were randomized to receive either an ACB with 0.75% ropivacaine or placebo (saline). The ropivacaine cohort had significantly lower VAS scores (40 vs. 60 points; $p = 0.01$) and morphine use (40 vs. 56 mg; $p = 0.006$) at 24 hours postoperatively than the placebo group. Nader et al[56] randomized 40 TKA patients to receive either a single injection bupivacaine ACB or a normal saline injection. Postoperative opioid use was lower in the bupivacaine cohort (48 vs. 60 mg; $p = 0.03$) compared with the control group, and the authors also noted that the bupivacaine group had a significantly lower pain burden at rest ($p = 0.009$). Hanson et al[67] also demonstrated lower morphine consumption and pain scores in 80 patients treated with ropivacaine versus placebo. However, they also noted that the treatment group had a longer ambulation distance (378 vs. 244 feet; $p = 0.034$), with no significant differences in quadriceps muscle strength when compared with the placebo cohort. Although other studies have conversely demonstrated weaker muscle function when compared with placebo, the literature supports that more muscle strength is preserved with ACB when compared with FNBs.[61]

The ACB may also allow for earlier ambulation when compared with the FNB. Shah and Jain[68] randomized 100 TKA patients to receive either ACB or FNB. The ACB group had faster functional recovery, as demonstrated by quicker timed up and go test results (51 vs. 180 seconds; $p < 0.05$) than the FNB block; however, there were no differences in pain scores.

In summary, the earlier studies demonstrated that ACB may provide comparable pain relief to FNB, while preserving greater motor function. They may also allow for lower opioid consumption compared with when no nerve block is administered.

Current Multimodal Analgesic Regimens

In recent years, there has been a shift toward the use of multimodal analgesic regimens to target multiple pain pathways while reducing narcotic consumption (►**Table 5**). Ranawat et al[70] publicized a multimodal pain regimen to improve postoperative pain, which included a combination of continuous postoperative epidural analgesia and adjunctive FNB for 48 hours, with supplemental morphine PCA.

Table 5 Multimodal analgesic regimens

Author (year)	Pain regimen	No. of patients	Pain	Range of motion < 90 deg	Percentage discharged home
Lavie et al[71] (2016)	Preoperative: 1. Cryoneurolysis 2. Decadron 3. ACB Intraoperative: 4. PAI—Marcaine/epinephrine Postoperative: 5. Acetaminophen 6. Celecoxib 7. Hydrocodone	N/A	N/A	N/A	N/A
Parvataneni et al[44] (2007)	Preoperative: 1. Celecoxib 2. Oxycodone Intraoperative: 3. PAI—bupivacaine, morphine, epinephrine, methylprednisolone Postoperative: 4. Ketorolac 5. Celecoxib 6. Oxycodone 7. Acetaminophen	31	Mean VAS: 4.3	N/A	55
Ranawat et al[70] (2003)	1. Postoperative epidural anesthesia 24–48 h 2. Adjuvant FNB 48 h 3. Morphine PCA 4. Opioid analgesia	181	Pain limiting activity: 13%	10%	N/A

Abbreviations: ACB, adductor canal block; N/A, not applicable; PAI, periarticular injection; PCA, patient controlled analgesia; VAS, visual analog scale.

Lavie et al[71] advocated a multimodal pain regimen that consisted of preoperative cryoneurolysis for 5 days, followed by an ACB on the day of surgery, intraoperative periarticular injections of bupivacaine with epinephrine, and postoperative scheduled acetaminophen, celecoxib, pregabalin, and hydrocodone/acetaminophen. Parvataneni et al[44] described a multimodal approach for pain management in total hip and knee arthroplasties that included pre-emptive celecoxib and oxycodone, intraoperative injection of bupivacaine, morphine sulfate, and methylprednisolone, and postoperative ketorolac, celecoxib, oxycodone, and acetaminophen. Pain scores were significantly lower in patients who received this protocol, compared with those who received FNB and PCA on PODs 1 to 3 ($p < 0.05$). Furthermore, 55% of the multimodal cohort was discharged home compared with 20% in the control group.

In summary, several multimodal analgesia regimens have been developed by combining the agents that have shown to be efficacious when used individually. These regimens have been proposed and studied in different centers, and therefore, cannot be compared with one another. Various multimodal therapies should be compared prospectively in the same patient population.

Novel Techniques

Liposomal Bupivacaine as Nerve Blocks

Liposomal bupivacaine is approved for administration into the surgical site but not for peripheral nerve blocks. In a two-part clinical study designed to meet the United States Food and Drug Administration standard for approval of analgesic agents, FNB with liposomal bupivacaine after TKA resulted in modestly reduced average pain and opioid use in the first 72 hours after surgery compared with placebo.[8] Wang et al[72] evaluated 341 TKA patients who received either an ACB with liposomal bupivacaine or a ropivacaine pain ball. The liposomal bupivacaine group had significantly lower pain scores at 36 hours postoperatively compared with the ropivacaine group (3.1 vs. 4l points; $p < 0.001$), as well as lower opioid use, although this was not significant (115 vs. 173 mg; $p = 0.08$). There were no significant differences in lengths of stay or cost between the two groups. A recent study included 52 adult patients who were randomized to receive either 5 mL of 0.25% bupivacaine immediately followed by 10 mL of liposomal bupivacaine 133 mg ($n = 26$) or 15 mL of 0.25% standard bupivacaine alone ($n = 26$) for an interscalene brachial plexus block.[73] The primary outcome (worst pain in the first postoperative week) was assessed by the Modified Brief Pain Inventory short form. Secondary outcomes were overall satisfaction with analgesia, functionality of the surgical arm, sleep duration, time to first opioid (tramadol) request, opioid consumption (mEq), sensory–motor block characteristics, and the occurrence of reported adverse effects. The study concluded that when used in interscalene brachial plexus blocks, liposomal bupivacaine added to standard bupivacaine may lower pain and enhance patient's satisfaction in the first postoperative week, even in the setting of multimodal analgesia for major shoulder surgery.

Cryoneurolysis

Cryoneurolysis has recently been introduced in the management of postoperative pain. It involves the use of cold therapy on terminal nerves.[71,74] A study in rats demonstrated that degeneration occurred distal to the freezing site, with preservation of the overall anatomical structure.[75] Regeneration of nerve endings was shown to occur ~6 weeks following therapy. Dasa et al[76] evaluated the use of percutaneous freezing of the infrapatellar branch of the saphenous nerve and femoral cutaneous nerve in 50 patients compared with 50 patients who did not receive this treatment prior to TKA. The authors noted that a smaller proportion of patients in the cryoneurolysis cohort had more than 2 days lengths of stay compared with the control group (6 vs. 67%; $p < 0.0001$). In addition, the treatment group had 45% lower narcotic consumption within 12 weeks postoperatively compared with the control cohort (2,069 vs. 3,764 mg; $p < 0.0001$). The cryoneurolysis cohort also had significantly greater reductions in the Knee Injury and Osteoarthritis Outcome Score symptom subscale score compared with the control group at 6 ($p = 0.004$) and 12 weeks ($p = 0.001$) postoperatively.

Conclusion

Achieving optimal pain control following TKA remains a challenge, given its subjective nature and patient variability. As a result, it is difficult to devise a "one fits all" analgesic regimen. In this analysis, we reviewed the use and efficacy of different modes of perioperative analgesia. Periarticular injections have shown to be efficacious with a remarkably favorable side-effect profile. The use of liposomal bupivacaine and/or its mixtures with bupivacaine is likely to play an increasingly important role in interventional pain management. There is a predictable positive correlation between adequate pain management and postsurgical recovery and rehabilitation, and a multimodal perioperative protocol with periarticular or perineural injections appears to be the most efficacious method.[1,69] Currently, research is being performed looking at the efficacy and safety of liposomal bupivacaine in peripheral nerve blocks, with the available data demonstrating promising significant advantages in accomplishing prolonged postoperative analgesia.[8,73,77–79]

Conflict of Interest
Dr. Mont, Dr. Kelly, and Dr. Elmallah are paid consultants for Pacira Pharmaceuticals Inc.

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